Amendments to the Claims

Claim 1 (Original): A method of diagnosing cleft lip and/or palate or other disease states associated with IRF6 dysfunction or dysregulation in a subject, comprising:

obtaining a biological sample from said subject; and

detecting a polymorphism in a IRF6 nucleic acid, wherein the presence of a polymorphism associated with cleft lip and/or palate or other disease state associated with an IRF6 dysfunction or dysregulation.

Claim 2 (Original): The method of claim 1, wherein said polymorphism is in exons 2-9 of said IRF6 encoding nucleic acid.

Claim 3 (Original): The method of claim 1, wherein said nucleic acid is a sequence which encodes a polypeptide sequence comprising amino acids 13-113 of SEQ ID NO:2, wherein said polypeptide comprises at least one polymorphism associated with an IRF6 dysfunction or dysregulation.

Claim 4 (Original): The method of claim 1, wherein said nucleic acid is a sequence which encodes a polypeptide sequence comprising amino acids 226-394 of SEQ ID NO:2, wherein said polypeptide comprises at least one polymorphism associated with an IRF6 dysfunction or dysregulation.

Claim 5 (Original): The method of claim 3, wherein said polymorphism is a change from an arginine to cysteine at amino acid residue 84 (Arg84Cys).

Claim 6 (Original): The method of claim 3, wherein said polymorphism is a change from an arginine to histidine at amino acid residue 84 (Arg84His).

Claim 7 (Original): The method of claim 5, wherein said polymorphism is characterized by a loss of contact with a DNA binding domain of IRF6.

Claim 8 (Original): The method of claim 6, wherein said polymorphism is characterized by a loss of contact with a DNA binding domain of IRF6.

Claim 9 (Original): A method of diagnosing an IRF6 dysfunction or dysregulation in a subject, said method comprising:

obtaining a biological sample from said subject;

detecting the presence of at least one polymorphism as set forth in Table 1 in IRF6 in said sample, wherein the presence of said polymorphism is indicative of said subject having an IRF6 dysfunction or dysregulation.

Claim 10 (Original): A method of diagnosing a susceptibility or propensity to Van der Woude syndrome, Poplitieal pterygium syndrome, or isolated cleft lip and/or palate in a subject, comprising:

obtaining a biological sample from said subject; and

detecting a polymorphism in an IRF6 encoding nucleic acid present in said sample, wherein the presence of said polymorphism in is indicative of said subject being susceptible to or having a propensity for Van der Woude syndrome, Poplitieal pterygium syndrome, or isolated cleft lip and/or palate.

Claim 11 (Withdrawn): A method of diagnosing a susceptibility to Van der Woude syndrome, Poplitieal pterygium syndrome, or isolated cleft lip and/or palate, comprising

obtaining a biological sample from said subject; and

detecting an alteration in the activity of a polypeptide encoded by an IRF6 gene in a test sample, in comparison with the activity of a polypeptide encoded by IRF6 gene in a control

sample, wherein the presence of an alteration in activity of the polypeptide in the test sample is indicative of a susceptibility to Van der Woude syndrome, Poplitieal pterygium syndrome, or isolated cleft lip and/or palate.

Claim 12 (Original): A method for screening a subject predisposed or susceptible an IRF6-related disorder associated with a genetic polymorphism in the IRF6 gene, said method comprising:

providing a biological sample from the subject; and

testing the sample for the presence of one or more nucleotide mutations from nucleotide positions 1-2171 of SEQ ID NO: 1, wherein, the presence of the mutation indicates that the subject is genetically predisposed to an IRF6-related disorder.

Claim 13 (Original): A method of diagnosing susceptibility to isolated cleft lip and/or palate in a subject, comprising:

obtaining a biological sample from said subject; and

detecting a polymorphism in a IRF6 gene product, wherein the presence of an amino acid change from a valine to an isoleucine at amino acid residue 274 (Val274Ile) in said gene product is indicative of said subject having a susceptibility to isolated cleft lip and/or palate.

Claim 14 (Original): A method for diagnosing susceptibility to isolated cleft lip and/or palate in an individual, comprising:

screening for an at-risk genotype in a IRF6 nucleic acid that is more frequently present in an individual susceptible to isolated cleft lip and/or palate (affected), compared to the frequency of its presence in a healthy individual (control), wherein the presence of the at-risk genotype is indicative of a susceptibility to isolated cleft lip and/or palate.

Claim 15 (Original): The method of claim 14, wherein said at-risk genotype is characterized as a VV genotype at allele 274 of an IRF6 gene product.

Claim 16 (Original): A method for diagnosing an individual at-risk for isolated cleft lip and/or palate associated with a V allele in an IRF6 gene product comprising:

providing a biological sample from said individual;

determining the genotype of said individual at nucleic acid corresponding to a V274I site of an IRF6 gene product, wherein an individual with two valine encoding alleles at the nucleic acid corresponding to said V274I site possess an at-risk genotype associated with isolated cleft lip and/or palate.

Claim 17 (Original): The method of claim 16, wherein a valine/valine (VV) encoding genotype is at an increased risk of isolated cleft lip and/or palate than an individual with an isoleucine/isoleucine (I/I) encoding genotype.

Claim 18 (Original): The method of claim 16, wherein a valine/valine (VV) encoding genotype is at an increased risk of isolated cleft lip and/or palate than an individual with a valine/isoleucine (VI) encoding genotype.

Claim 19 (Original): A method for screening a subject predisposed or susceptible to Van der Woude syndrome, Poplitieal pterygium syndrome, or isolated cleft lip and/or palate associated with a genetic polymorphism in the IRF6 gene, said method comprising:

providing a biological sample from the subject; and

testing the sample for the presence of one or more nucleotide mutations from nucleotide positions 1-2171 of SEQ ID NO: 1, wherein, the presence of the mutation as shown in Table 1 indicates that the subject is genetically predisposed to Van der Woude syndrome, Poplitieal pterygium syndrome, or isolated cleft lip and/or palate.

Claim 20 (Original): A method of determining a risk for an IRF6 dysfunction or dysregulation or propensity thereto in a subject, said method comprising:

obtaining a biological sample from said subject;

analyzing the IRF6 nucleic acid in said sample; and

determining the presence of at least one mutation as set forth in Table 1 of IRF6, wherein the presence of said mutation is indicative of a risk for an IRF6 dysfunction or dysregulation or propensity thereto in said subject.

Claim 21 (Original): The method of claim 20, wherein said IRF6 dysfunction or dysregulation is selected from the group consisting of: Van der Woude syndrome, Poplitieal pterygium syndrome, and isolated cleft lip and/or palate.

Claim 22 (Original): A method of identifying a polymorphism associated with an IRF6 dysfunction or dysregulation comprising: isolating a nucleic acid of SEQ ID NO:1 from a plurality of subgroup of subjects, wherein one subgroup has no prevalence for a IRF6 associated disease and at least one or more subgroups which do have a prevalence for a IRF6 associated disease; and identifying a polymorphism as set forth in Table 1 by comparing the nucleotide sequence of the nucleic acid of the one subgroup having no prevalence for an IRF6 associated disease with the at least one or more subgroups having a prevalence for an IRF6 associated disease.

Claim 23 (Original): A method of detecting a polymorphism associated with an IRF6 dysfunction or dysregulation comprising:

obtaining a biological sample from said subject; and

detecting a nucleic acid molecule comprising an IRF6 nucleic acid having the nucleotide sequence of SEQ ID NO:1 and comprising at least one polymorphism as shown in Table 1.

Claim 24 (Original): The method of claim 23, wherein said IRF6 dysfunction or dysregulation is selected from the group consisting of: Van der Woude syndrome, Poplitieal pterygium syndrome, and isolated cleft lip and/or palate.

Claim 25 (Withdrawn): A method of identifying an agent which modulates activity of a polypeptide encoded by an IRF6 nucleic acid, wherein said polypeptide comprises an amino acid sequence as depicted in SEQ ID NO:2 and comprises at least one polymorphism as shown in Table 1 comprising:

contacting said polypeptide variant with an agent to be tested;

assessing the level of activity of the IRF6 variant polypeptide; and

comparing the level of activity with a level of activity of said variant polypeptide in the absence of the agent, wherein if the level of activity of the polypeptide in the presence of the agent differs, by an amount that is statistically significant from the level in the absence of the agent, then the agent is an agent that modulates activity of a variant IRF6 polypeptide.

Claim 26 (Withdrawn): A method of identifying an agent which alters expression of a variant IRF6 nucleic acid, comprising:

contacting a variant nucleic acid comprising SEQ ID NO:1 and comprising at least one polymorphism at shown in Table 1 with an agent to be tested;

assessing the level of expression of said variant nucleic acid; and

comparing the level of expression with a level of expression of said variant nucleic acid in the absence of the agent, wherein if the level of expression of the nucleotide in the presence of the agent differs, by an amount that is statistically significant, from the expression in the absence of the agent, then the agent is an agent that alters expression of a variant IRF6 nucleic acid.

Claim 27 (Withdrawn): A method of identifying and obtaining an inhibitor of the activity of a polypeptide, or a derivative, or fragment thereof comprising the amino acid sequence of SEQ ID NO:2 which comprises at least one polymorphism as shown in Table 1, comprising:

contacting said polypeptide, or derivative, or fragment thereof with a test agent for inhibiting activity, in the presence of compounds that provide a detectable symbol in response to test agent activity; and

detecting the presence or absence of a signal or increase or decrease of a signal generated from inhibiting activity, wherein the absence or decrease of the signal is indicative inhibiting activity of said polypeptide.

Claim 28 (Original): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of said IRF6 nucleic acid to said immobilized targets on said solid support.

Claim 29 (Original): The method of claim 28, wherein a binding of a variant IRF6 nucleic acid to said immobilized targets on said solid support is indicative of the presence, absence, or prevalence of an IRF6 dysfunction or dysregulation.

Claim 30 (Original): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of an IRF6 nucleic acid comprising the nucleotide sequence of SEQ ID NO:1 and comprising at least one polymorphism as shown in Table 1.

Claim 31 (Original): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of a vector, wherein said vector comprises an isolated nucleic acid comprising SEQ ID NO:1 and comprising at least one polymorphism as shown in Table 1, operatively linked to a regulatory sequence to said

immobilized targets on said solid support.

Claim 32 (Withdrawn): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of a recombinant host cell, present in said sample.

Claim 33 (Withdrawn): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of an isolated polypeptide encoded by an IRF6 nucleic acid present in said sample, said polypeptide comprising:

(a) the amino acid sequence as depicted in SEQ ID NO:2 which comprises at least one polymorphism as shown in Table 1;

(b) the amino acid sequence as depicted in SEQ ID NO:2 which comprises at least two polymorphisms as shown in Table 1;

(c) an amino acid sequence which is greater than about 90% identical to an amino sequence of SEQ ID NO:2 and comprising at least one polymorphism as shown in Table 1; and

(d) an amino acid sequence which is greater than about 95% identical to an amino acid sequence of SEQ ID NO:2 and comprising at least one polymorphism as shown in Table 1.

Claim 34 (Withdrawn): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of an antibody, or a fragment thereof, that specifically binds to the polypeptide encoded by an IRF6 nucleic acid comprising:

(a) the amino acid sequence as depicted in SEQ ID NO:2 which comprises at least one polymorphism as shown in Table 1;

(b) the amino acid sequence as depicted in SEQ ID NO:2 which comprises at least two polymorphisms as shown in Table 1;

(c) an amino acid sequence which is greater than about 90% identical to an amino sequence of SEQ ID NO:2 and comprising at least one polymorphism as shown in Table 1; and

(d) an amino acid sequence which is greater than about 95% identical to an amino acid sequence of SEQ ID NO:2 and comprising at least one polymorphism as shown in Table 1.

Claim 35 (Original): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of a nucleic acid molecule comprising exons 2-9 of IRF6 having a nucleotide sequence comprising SEQ ID NO:1 and comprising at least one polymorphism associated with Van der Woude syndrome, Poplitieal syndrome, and isolated cleft lip and/or palate in any one of said exons.

Claim 36 (Original): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of an IRF6 nucleic acid having a nucleotide sequence depicted in SEQ ID NO:1, wherein said nucleotide sequence encodes a polypeptide sequence comprising amino acids 13-113 of SEQ ID NO:2, wherein said polypeptide comprises at least one polymorphism as shown in Table 1.

Claim 37 (Original): The method of claim 1, wherein said detecting comprising contacting said sample with a solid support under conditions allowing interaction of an IRF6 nucleic acid having a nucleotide sequence depicted in SEQ ID NO:1, wherein said nucleotide sequence encodes a polypeptide sequence comprising amino acids 226-394 of SEQ ID NO:2, wherein said polypeptide comprises at least one polymorphism as shown in Table 1.

Claim 38 (Withdrawn): A diagnostic composition for detecting the predisposition to an IRF6 dysfunction or dysregulation, the composition comprising at a nucleic acid comprising SEQ ID NO:1 and comprising at least one polymorphism, and a carrier.

Claim 39 (Withdrawn): The diagnostic composition of claim 38 comprising a nucleic acid sequence comprising SEQ ID NO:1 and comprising at least one polymorphism as shown in Table 1, and a carrier.

Claim 40 (Withdrawn): A transgenic non-human animal comprising

(a) a nucleic acid molecule comprising an IRF6 nucleic acid having the nucleotide sequence having SEQ ID NO:1 and comprising at least one polymorphism as shown in Table 1;

(b) a nucleic acid molecule comprising an IRF6 gene, the nucleotide sequence of SEQ ID NO:1 encoding a polypeptide comprising an amino acid sequence as depicted in SEQ ID NO:2 and comprises at least one polymorphism associated as shown in Table 1.

Claim 41 (Withdrawn): An isolated nucleic acid molecule comprising:

(a) a nucleic acid molecule comprising an IRF6 nucleic acid having the nucleotide sequence of SEQ ID NO:1 and comprising at least one polymorphism as shown in Table 1;

(b) a nucleic acid molecule comprising an IRF6 nucleic acid having the nucleotide sequence of SEQ ID NO:1 and comprising at least two polymorphism as shown in Table 1; and

(c) a nucleic acid molecule comprising an IRF6 gene, the nucleotide sequence of SEQ ID NO:1 encoding a polypeptide comprising an amino acid sequence as depicted in SEQ ID NO:2 and comprises at least one polymorphism associated as shown in Table 1.

Claim 42 (Withdrawn): A vector comprising an isolated nucleic acid molecule comprising SEQ ID NO:1 and comprising at least one polymorphism shown in Table 1, operatively linked to a regulatory sequence.

Claim 43 (Withdrawn): A recombinant host cell comprising the vector of claim 42.

Claim 44 (Withdrawn): An isolated nucleic molecule comprising an IRF6 nucleic acid having a nucleotide sequence depicted in SEQ ID NO:1, wherein said nucleotide sequence encodes a polypeptide sequence comprising amino acids 13-113 of SEQ ID NO:2, wherein said polypeptide comprises at least one polymorphism as shown in Table 1.

Claim 45 (Withdrawn): An isolated nucleic molecule comprising an IRF6 nucleic acid having a nucleotide sequence depicted in SEQ ID NO:1, wherein said nucleotide sequence encodes a polypeptide sequence comprising amino acids 226-394 of SEQ ID NO:2, wherein said polypeptide comprises at least one polymorphism as shown in Table 1.

Claim 46 (Withdrawn): The isolated nucleic acid molecule of claim 44, said polymorphism is a change from arginine to a cysteine at amino acid residue 84 (Arg84Cys).

Claim 47 (Withdrawn): The isolated nucleic acid molecule of claim 46, said polymorphism is a change from a cytosine to a thymine at nucleotide position 250 (C250T).

Claim 48 (Withdrawn): The isolated nucleic acid molecule of claim 44 said polymorphism is a change from an arginine to a histidine at amino acid residue 84 (Arg84His).

Claim 49 (Withdrawn): The isolated nucleic acid molecule of claim 48, said polymorphism is a change from a guanine to an adenine at nucleotide position 251 (G251A).

Claim 50 (Withdrawn): An isolated nucleic acid molecule comprising: exons 2-9 of an IRF6 nucleic acid comprising SEQ ID NO:1, wherein at least one has at least one polymorphism as shown in Table 1.

Claim 51 (Withdrawn): An isolated polypeptide encoded by an IRF6 nucleic acid comprising:

(a) the amino acid sequence as depicted in SEQ ID NO:2 which comprises at least one polymorphism as shown in Table 1;

(b) the amino acid sequence as depicted in SEQ ID NO:2 which comprises at least two polymorphisms as shown in Table 1;

(c) an amino acid sequence which is greater than about 90% identical to an amino sequence of SEQ ID NO:2 which comprises at least one polymorphism as shown in Table 1; and

(d) an amino acid sequence which is greater than about 95% identical to an amino acid sequence of SEQ ID NO:2 which comprises at least one polymorphism as shown in Table 1.

Claim 52 (Withdrawn): A fusion protein comprising the polypeptide of claim 51.

Claim 53 (Withdrawn): An antibody, or an antibody fragment thereof, that specifically binds to the polypeptide of claim 51.

Claim 54 (Withdrawn): An antibody, or antibody fragment thereof that specifically binds to the polypeptide of claim 44.

Claim 55 (Withdrawn): An antibody or antibody fragment thereof that specifically binds to the polypeptide of claim 45.

Claim 56 (Withdrawn): An isolated nucleic acid comprising at least 20-50 contiguous nucleotides, wherein said nucleic acid comprises the nucleotide sequence of SEQ ID NO:1 and comprises at least one polymorphism as shown in Table 1.

Claim 57 (Withdrawn): The nucleic acid molecule of claim 41, wherein the nucleic acid is DNA.

Claim 58 (Withdrawn): The nucleic acid molecule of claim 41, wherein the nucleic acid is RNA.

Claim 59 (Withdrawn): The nucleic acid of claim 56, wherein the nucleic acid is DNA.

Claim 60 (Withdrawn): The nucleic acid of claim 56, wherein the nucleic acid is RNA.

Claim 61 (Withdrawn): An isolated polypeptide encoded by an IRF6 nucleic acid comprising: the amino acid sequence as depicted in SEQ ID NO:2, wherein said polypeptide sequence comprises a polymorphism of valine to isoleucine at amino acid residue 274 (V274Ile).

Claim 62 (Withdrawn): A pharmaceutical composition comprising the polymorphic nucleic acid of claim 41 and a physiologically acceptable carrier.

Claim 63 (Withdrawn): A pharmaceutical composition comprising the vector of claim 42, and a physiologically acceptable carrier.

Claim 64 (Withdrawn): A pharmaceutical composition comprising the polypeptide of claim 51, and a physiologically acceptable carrier.

Claim 65 (Withdrawn): A pharmaceutical composition comprising the fusion protein of claim 52, and a physiologically acceptable carrier.

Claim 66 (Withdrawn): A pharmaceutical composition comprising the antibody of claim 53 and a physiologically acceptable carrier.